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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,605	FIEDLER ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *14,15,17-25,29-41 and 43-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,16,26-28 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Examiner of record has changed. Please address all subsequent correspondence to Examiner Michael Borin, AU 1631.

Status of Claims

2. Amendment filed 05/16/2005 is acknowledged. Claims 1-45 are pending. With respect to election of species of proteins, while the originally elected species were bovine gamma crystalline [1], applicant now points to SEQ ID No. 21 as the elected species. Since there is no SEQ ID Nos in the specification, it is not possible to judge whether peptides of SEQ ID Nos 19 or 21 are related to the elected species, bovine gamma crystallin. Consequently, claim 15 is withdrawn from consideration. In addition, claims 14,17-25,29-41,43-45 remain withdrawn from consideration.

Claims 1-13,16,26-28,42 are addressed to the extent they read on the elected species.

3. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn. The following rejections are either reiterated or newly applied and constitute the complete set presently being applied to the instant application.

Sequence Listing

1 Lipocalin was added by the previous Examiner as another protein species.

4. It is noted that peptide and nucleic acid sequences in specification, figures and claims are not followed by corresponding SEQ ID Nos. 37 CFR 1.821 requires that:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

See MPEP 2422.

Applicant is requested to provide SEQ ID Nos for peptide sequences in specification and claims.

Specification

5. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Specification does not provide support for Seq ID numbers used in claims 12,15, and for amino acid positions recited in claim 12.

Claim Rejections - 35 USC 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. (New Matter) Claims 1-13,16,26-28,42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In

claims 1,3-6, the phrase "located within" introduce new matter as it brings in a distance limitation which was not described in specification.

7. (Written Description) Claims 1-13,16,26-28,42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are directed to any protein with beta sheet structure having mutated amino acid residues located on the surface of the protein, wherein protein appropriated novel functional features (e.g., new binding activity) due to the mutations. Note, that the claims are directed to a product, not to a method of making the product. The only embodiment described in the specification is mutated bovine gamma-II-crystallin. Specification provides a laundry list of proteins that have beta-sheet structure and thus can be mutagenized (see p. 6, lines 11-13); however, neither of them, except for bovine gamma-II-crystallin has been demonstrated to be mutagenized to arrive at a mutant having new functional properties. Bovine gamma-II-crystallin is not a sufficient representative of a vast genus of beta-sheet comprising proteins, and generally stated functional limitations do not provide sufficient structural characteristics to define the genus of the claimed proteins.

The inventor must be able to describe the item to be patented with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique method that makes it worthy of patent protection. The reader can certainly appreciate the goal but establishing goals does not make a patent. As the Court of

Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993). To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; *see also Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"). There is no demonstration in the specification that besides bovine gamma II crystallin mutagenized to appropriate binding affinity for BSA-estradiol-17-hemisuccinate, applicants generated any other protein which, being mutagenized, appropriated new functional characteristics as claimed or, at least another mutagenized crystallin protein having new characteristics other than ability to bind BSA-estradiol-17-hemisuccinate. Similarly to *In re Wilder*, 736 F.2d 1516 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 1209 (1985) the specification did "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."

8. Claims 1-13,16,26-28,42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for crystallin protein mutants obtained by phage display system described in the specification, does not reasonably provide

enablement for other proteins with beta sheet structure in which amino acids located on surface beta strands are altered by substitution, deletion, etc.

The disclosure is directed to crystallin mutants obtained by highly selective method of using phage display system to screen for proteins (crystalline in particular) with *de novo* binding properties. However, the breadth of the claims encompasses any protein with beta sheet structure in which at least one surface amino acid residue is altered by substitution, deletion, etc. There is no guidance on how to use a random protein having beta sheet structure in which amino acids located on surface beta strands are altered. For example, claim 12, which is most specific in addressing structural changes, is directed to protein SEQ ID No. 22 with particular substitutions. However, as stated in the rejections over den Dunnen et al. or Graw et al. al (see paragraph #11 below) proteins with such substitutions read on other gamma crystallins (which have no binding properties at all–see specification, p. 4, first full paragraph), rather than on a mutagenized gamma crystalline with novel binding properties. Specification does not provide sufficient nexus between structural and functional characteristics as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC 102.

9. Claims 1-6, 10,11,1316,27,28,42 are rejected under 35 U.S.C. 102(a) as anticipated by Beste et al.

Beste teaches that lipocalins is a family of diverse proteins that normally serve for the storage or transport of physiologically important compounds. Lipocalins share a conserved β-barrel of eight antiparallel β-strands as their central folding motif. At one end of this supersecondary structure four loops connect each pair of β-strands and form the entrance to the binding pocket. The binding site is formed by four loops on top of an eight-stranded β-barrel. p. 1898. 16 residues spread across the four loops and adjoining parts of the β-barrel of a lipocalin from *Pieris brassicae*, the bilin-binding protein (BBP), were selected and subjected to random mutagenesis. p. 1900, right column. The 16 positions were mutagenized in a polymerase chain reaction and a genetic library with $3.7 \cdot 10^8$ independent transformants was obtained. Out of those, four variants having a new feature, ability to bind fluorescein, a fluorophore and immunological hapten, were selected. p. 1901, left column. The resulting β-sheet structured proteins anticipated the various possible combinations of amino acids to be mutagenized as recited in claims 3-6, 10,11,13,16,27,28,42. The composition of claim 16 is also anticipated by solution of ELISA binding assay described in the reference (p. 1900, left column).

Response to arguments

First, applicant argues that Beste refernce does not teach creation of synthetic binding site *de novo*. The claims are not directed to methofd opf making; rather the claims are directed to a product and the product is anticipated by Beste references as explained in the rejection.

Second, applicant argues that the reference does not disclose element of proviso (ii) of claim 1. Examiner disagrees. Lipocalin which had binding affinity to its ligand,

biliverdin IX, has acquired a new binding affinity to another hapten, fuorescein. See p. 1902, bottom.

Third, applicant argues that the subject matter of claim 1 "excludes the use of naturally occurring binding sites". No such exclusion was found in the text of the claim.

Further, applicant discusses that the novelty of the invention is the use of crystallins. However, this rejection is directed to broad claims which are not limited to crystallin. The rejection addresses lipocalins.

10. Claims 1,2,7-9,11,26,27,42 are rejected under 35 U.S.C. 102(b) as anticipated by Chirgadze et al.

Chirgadze et al describe bovine gamma crystallin (i.e, the protein species elected by applicant) which is a protein containing β-sheet motif (see p. 717, Figure 4). Combination of two sequential motifs in crystallin results in domain structure with eight β-strands which form two antiparallel β-sheets. p. 716, last paragraph. The crystallin described in the reference contains mutations involving surface residues Leu51, Ile103, and His155, and the reference suggests that these mutations will contribute to the intermolecular behavior of gamma crystallin. See abstract. Thus, the reference reads on the protein with β sheet structure in which surface amino acid residues located on at least 2 β-strands are mutated. The reference teaches the crystallin protein that meets the structural limitation claimed. Although the reference does not teach the functional limitation of the protein, such a limitation would be inherent in the peptide since it meets the structural limitations of the claim. Where the claimed and prior art products are

identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 195 USPQ 430, 433 (CCPA 1977). When the reference discloses all the limitations of a claim except a property or function, and the examiner cannot determine whether or not the reference inherently possesses the properties which anticipate or render obvious the claimed invention, the burden of proof shifts to applicant. In re Fitzgerald et al. 619 F.2d 67, 205 USPQ 594, (CCPA 1980). Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re* Best, 562 F.d. 1252, 195 USPQ 430 (CCPA 1977) and *In re* Fitzgerald et al., 205 USPQ 594. Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 195 USPQ 430, 433 (CCPA 1977).

11. Claims 1,2,7-12,26-28,42 are rejected under 35 U.S.C. 102(b) as anticipated by den Dunnen et al. (Database PIR_79, Accession Number B24060; J. Mol. Biol., 189,37-46,1986) or den Dunnen et al (Database PIR_79, Accession Number A24060; Gene, 38, 197-204, 1985) or Graw et al. al (Database UniProt, Accession Number P04344; Gene,136, 145-156, 1993).

The referenced compounds are gamma crystallins from rat, human and mouse, respectively, which read on crystalline of claim 12 in which at least one of the amino acid residues recited in claim 12 is replaced with another amino acid residue. Similarly to the rejection over Chirgadze above, the references teach crystallin protein that meets the structural limitation claimed. Although the references do not teach the functional limitations of the protein, such a limitations would be inherent in the peptide since it meets the structural limitations of the claim. Further, since each of the cited gamma crystallins is from another source it is assumed to have different binding capabilities to bind to rat, human and mouse antibodies respectively, and differ in this respect from bovine gamma crystallin.

Conclusion.

12. No claims are allowed

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571)272-0713. The examiner can normally be reached on 9 am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Borin
Primary Examiner
Art Unit 1631

mlb